FDA-2005-E-310

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May 24, 2007

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Request for Revision of Regulatory Review Period
for KEPIVANCE
Docket No. 2005E-0245

Dear Sir or Madam:

Novartis Vaccines and Diagnostics, Inc., the successor to Chiron Corporation, through undersigned counsel, hereby requests reconsideration and revision of the Regulatory Review Determination published in the Federal Register on April 2, 2007 (72 Fed. Reg. 156999). We believe that date chosen by FDA as the date of submission of the KEPIVANCE (palifermin) BLA should be the date that the first segment of that application was submitted.

In accordance with 21 C.F.R. § 60.24(a), the following information is provided:

(1) The Type of Action Requested

It is respectfully requested that the "date the application was initially submitted with respect to the human biological product under section 505(b) of the act"[1] be corrected from the June 15, 2004 date given in the Notice to the May 14, 2004 date claimed by Applicant in the original Request for Extension of Patent Term, for at least the reasons detailed below, and that the Regulatory Review Period be recalculated accordingly.

(2) The Identity of the Product

[1] There should also be a technical correction, in that the submission was under Section 351 of the Public Health Service Act, rather than section 505(b) of the Food, Drug, and Cosmetic Act ("FDCA").

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The product for which this regulatory review period was determined is KEPIVANCE (palifermin).

(3) The Identity of the Applicant

The Applicant on the Request for Extension of Patent Term is Chiron Corporation, a corporation organized and existing under the laws of the State of Delaware. Novartis Vaccines and Diagnostics, Inc is the successor to Chiron Corporation. This Request for Revision is being filed on behalf of Applicant.

(4) The FDA Docket Number

The FDA Docket Number is Docket No. 2005E-0245.

(5) The Basis for the Request for Revision, Including any Documentary Evidence.

Chiron (now Novartis) is the patent holder for a patent covering KEPIVANCE (palifermin). Its licensee Amgen submitted the Biologics License Application ("BLA") for KEPIVANCE under section 351 of the Public Heath Service Act. At page 6 of Applicant's Request for Extension of Patent Term Pursuant to 35 U.S.C. § 156, Applicant explained that this BLA was reviewed by FDA as part of its "Fast Track" program[2], and thus was submitted in two reviewable units. Reviewable Unit 1 of the BLA was submitted to FDA on May 14, 2004, and Reviewable Unit 2 of the BLA was submitted to FDA on June 15, 2004.

In accordance with 35 U.S.C. §156(g)(1)(B), a crucial determination in the calculation of the Regulatory Review Period for a human biological product, such as KEPIVANCE (palifermin), is the date an application under section 351 was "initially submitted" to FDA. The Regulatory Review Determination published in the Federal Register on April 2, 2007 (F.R. 72 No. 62 at 156999) chooses the June 15, 2004 date of

[2] FDA sent a letter granting "Fast Track" designation section 506 of the Federal Food, Drug, and Cosmetic Act on December 31, 2003, Appendix A.

the submission of Reviewable Unit 2 as the date the application was "initially submitted," rather than the earlier submission on May 14, 2004 of Reviewable Unit 1.

We believe this was the wrong choice. FDA has already, in a different but directly relevant context, concluded that the BLA was submitted on the May 14 date. The FDCA specifically directs that user fees "shall be due upon submission of the application or supplement." Section 736(a)(1)(B) (emphasis added). FDA has no authority to require that such fees be paid before submission of the application.

Here, FDA asked for payment of the full BLA user fee at the time of the May 14 first submission.[3] Amgen, the applicant, paid that fee at the time of the May 14 submission. FDA's request for payment was presumably pursuant to FDCA Section 506(c)(1)(B), which itself evidences the Congressional understanding that the initial Reviewable Unit would be a "submission" under the law. That section says that FDA will commence review of an advance submission only after the applicant "pays any fee that may be required under section 736." (Emphasis added.) As noted, no fee is required under section 736 except "upon submission" of the BLA.

While we believe that the statute is clear that the date of the initial Reviewable Unit is the date of submission of the BLA, it is possible that FDA considers the later date as the date of submission because of a concern not to start the review clock when the first Reviewable Unit is submitted. Considering the date of the first Reviewable Unit as the date of submission would not, however, require starting the review clock when it is received. That clock would presumably start with the complete submission of the BLA. Conversely, the patent extension provision and the user fee provision do not require the complete submission, but rather focus on the initial submission.

To the extent that FDA considers the statutory term "initial submission" ambiguous, we ask FDA to reconsider its interpretation of that term in the context of Fast Track submissions. A reasonable understanding of the rationale for assigning significance to the BLA submission date is that it marks the termination of the IND testing phase of the development of the drug and begins the phase during which FDA is reviewing the data that have been developed during the testing phase. FDCA Section 506(c) provides that "[i]f the Secretary determines, after preliminary evaluation of clinical data submitted by the sponsor, that a fast track product may be effective, the

[3] *See* Record of Regulatory Contact (May 12, 2004), Appendix B.

Secretary shall evaluate for filing, and may commence review of portions of, an application for the approval of the product before the sponsor submits a complete application." (Emphasis added.)

To facilitate this review, FDA has explained that the Agency will generally accept for submission only a complete section of an application, that "will be in a form adequate to have been included in a complete BLA or NDA submission." *Guidance for Industry Fast Track Drug Development Programs -- Designation, Development, and Application Review*, page 13 (July 2004). As such, in accordance with FDA Guidance, each submission under a Fast Track program should be in a form sufficiently complete to allow for a substantive review of that section. FDA's regulation concerning patent term extensions explicitly contemplates situations in which all of the information necessary for approval may not be submitted in the first submission and addresses how the date of initial submission should be computed in that circumstance. It explains that "For purposes of determining the regulatory review period for any product, a marketing application . . . is *initially submitted* on the date it contains sufficient information to allow FDA to commence review of the application." 21 C.F.R. § 60.22(f) (second emphasis added). Thus, the BLA here was initially submitted when it contained sufficient information to allow the review to begin, i.e., the date of submission of the first Reviewable Unit.

Records of teleconferences with FDA underscore that the first Reviewable Unit of this BLA, submitted on May 14, 2004, contained sufficient information to allow FDA to commence review. They show that review had in fact been initiated prior to the submission of the second Reviewable Unit. For instance, the record of a telecon that took place between the BLA applicant and FDA on May 24, 2004 indicated that the pre-clinical RU (i.e., the first Reviewable Unit) had been loaded for review, and that the FDA review team had received training.[4] It is thus clear that FDA had initiated review of the first Reviewable Unit to some extent prior to submission of the second Reviewable Unit on June 15, 2004. As such, the approval phase for KEPIVANCE (palifermin) had in fact been initiated upon submission of the first Reviewable Unit, and prior to submission to the second Reviewable Unit.

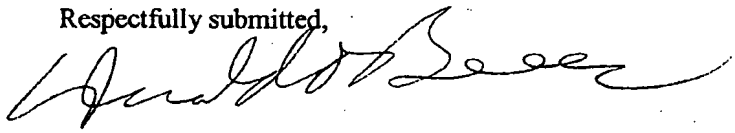
[4] *See* attached Record of Regulatory Contact (May 24, 2004), Appendix C.

We thus respectfully suggest that FDA consider the date of the first submission of the first Reviewable Unit for a drug, such as this one, submitted pursuant to the Fast Track program to be the date of "initial submission" of the application for purposes of patent term extension. Indeed, as a matter of public policy, it is hard to see why the FDA should choose to interpret the statute in a way to diminish the statutory incentives for development of the type of important new drug that would qualify for Fast Track consideration. Instead, development of such potentially breakthrough products should be encouraged.

Applicant therefore requests that the regulatory review period determination for KEPIVANCE (palifermin) be revised to correct the "date the application was initially submitted with respect to the human biological product under section 351" from the June 15, 2004 date given in the Notice to the May 14, 2004 date claimed by Applicant in the original Request for Extension of Patent Term.

Applicant further requests that the length of the regulatory review period be recalculated to take into account the corrected application submission date.

Respectfully submitted,



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Re: Request for Revision of Regulatory Review Period
for KEPIVANCE
Docket No. 2005E-0245:
Clarification concerning confidentiality

Dear Sir or Madam:

The Request of Revision that we submitted today attaches as appendices B and C two documents. Those documents contain language that suggests that they are confidential. This letter clarifies that those documents are not to be considered confidential and may be placed in the public record.

Respectfully submitted,

Donald O. Beers
Milan M. Vinnola

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